need of such treatment an effective amount of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl amine or a pharmaceutically acceptable salt thereof.

Please change the dependency of claim 14 to depend on claim 19.

Remarks

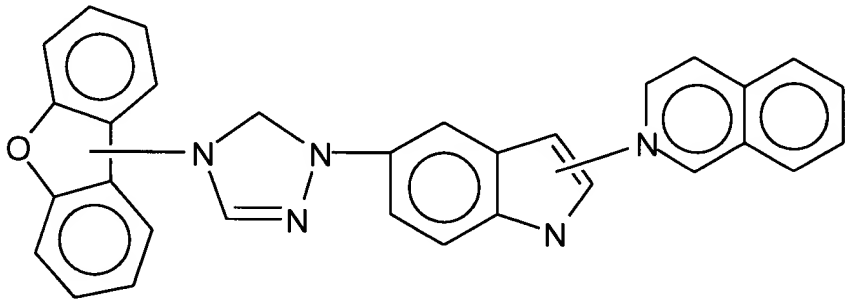
Claims 9 through 12, 14, and newly-added claim 19 are pending in this application.

The new compounds described in this application are useful as 5-HT$_1$ receptor agonists, which exhibit selective vasoconstrictor activity and are useful in the treatment of migraine and associated clinical conditions,.

Examiner states --

> Confirmation and correction is hereby made with regard to the election of example 5, claim 6, p. 100 lines 25-26, N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-11+indol-2-yl]ethylamine. This oversight is regretted.
>
> The improper Markush rejection of claims 1-8 is maintained for the following reasons:
>
> 1. In claim 6, the imidazolyl, tetrazolyl benzothiophenyl etc. compounds which are not in the now amended claim 1 have not been elected. A 112 fourth paragraph rejection will be made subsequently.
> 2. The propriety of Markush grouping finds antecedent basis in MPEP 803.02 where it states: "Broadly, unity of invention exists where compounds include within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility".
>
> The alleged triazolylindolyl structure, being the common feature for the utility, is not a substantial structural feature for such claimed compounds e.g.

claim 6)



for which, the other heterocyclic moieties constitutes major structural feature of the compounds.

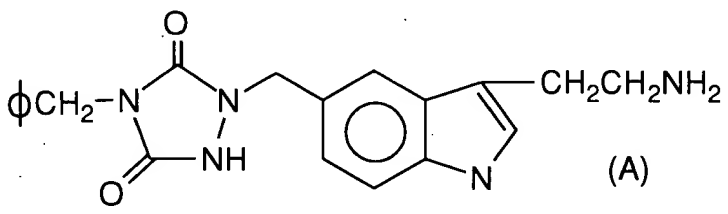
In addition, it is known in the indolyl amine, 5HT binding compound art, that small structural changes of the indolylamine compounds will result in drastic loss of biological activity (see Glennon cited on 1449, p. 6 last para.). In absence of factual evidence, there is insufficient support that all the diversified heterocyclic substituted compound i.e. "a heterocyclic group containing up to 18 carbon atoms and at least one heteroatom selected from oxygen, nitrogen and sulfur" would share the same utility as example 5. --

The Examiner's position is respectfully traversed.

Since claims 1 through 8 are being canceled without prejudice, the above Examiner's rejection is deemed moot and reconsideration is respectfully requested.

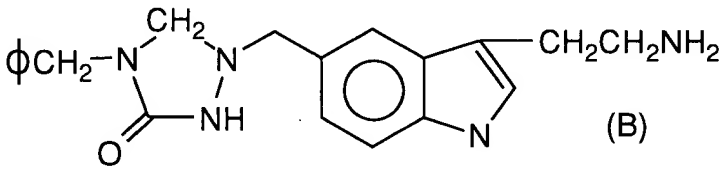
Examiner is maintaining the rejection of claim 1 under 35 USC 103 allegedly as being unpatentable over Robertson EP 313,397 for the following reasons --

The examiner regrets the error of misdrawing the bondings of comp. 24 of Robertsons'. Applicants' drawing on p. 12 of the amendment (Paper No. 5) is correct. Robertson's example 24 is



(A)

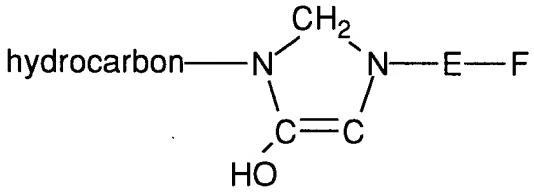
which is tantamount to:



(B)

O

(based on generic teaching $Z=Z^1$=C- or -CH_2) which is applicants' compound when X, Z, V are N, W, Y and C, A_1-OH at W, A^2=hydrocarbon at X that is



(C)

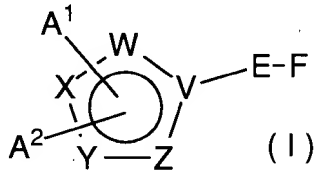
which is the tautomeric form of (B).

The arguments that applicants' compound are patentably distinct from Robertsons' triazolyl compounds in that applicants' triazolyl ring is always aromatic is incorrect. So far as claim 1 is concerned, both aromatic and non-aromatic rings are encompassed. Therefore, the rejection is maintained. --

Since claim 1 is being canceled, the above Examiner's rejection is deemed to be moot and reconsideration is respectfully requested.

However, the Examiner's above comments regarding the structural chemistry are not correct and comments are being made to correct the record.

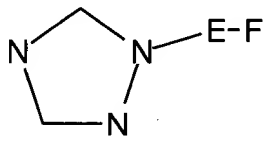
The applicants' compounds, as defined in claims 1 through 8, are all heteroaromatic. This is supported in the specification on page 2, lines 1 through 16, where it is stated:



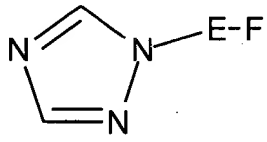
(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; (emphasis added)

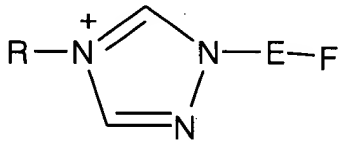
Notice that in claim 1 there must be two non-adjacent double bonds in the hetero-aromatic ring. Thus, when X, V and Z are all N, this results in the following ring structure without the double bonds:



There is only one way of introducing two double bonds into this 5-membered ring without forming quaternary ammonium ions:



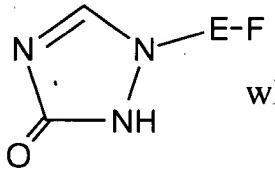
Notice that substitution of the 4-N ring atom will result in a quaternary compound which is outside the scope of the claims and not included; i.e.:



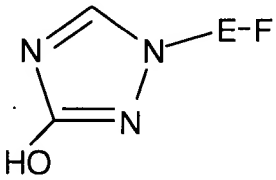
Thus, two N atoms cannot be substituted and still maintain the heteroaromatic, non-quaternary character of applicants' compounds.

Structures (i) and (ii) of Robertson are not pertinent to this discussion since they only contain 2 ring nitrogens. However, structures (iii) and (iv) of Robertson are pertinent since they are not heteroaromatic, not quaternary and are heteroaliphatic.

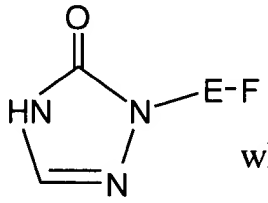
The discussion of Examiner's comments regarding Katritzky and tautomerism is complex in terms of which structures can be heteroaromatic. To start with, consider applicants' structures where only one ring nitrogen is substituted, and where hydroxy groups are present on the ring;



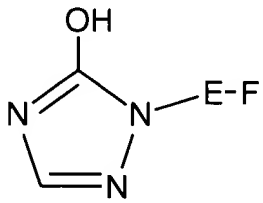
which can tautomerize to



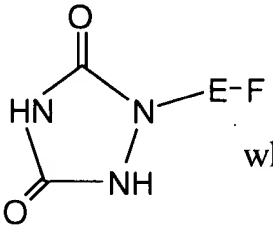
I I-A



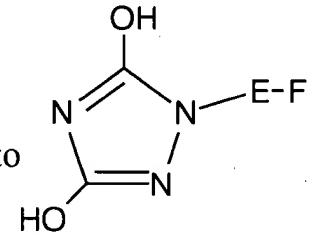
which can tautomerize to



II II-A



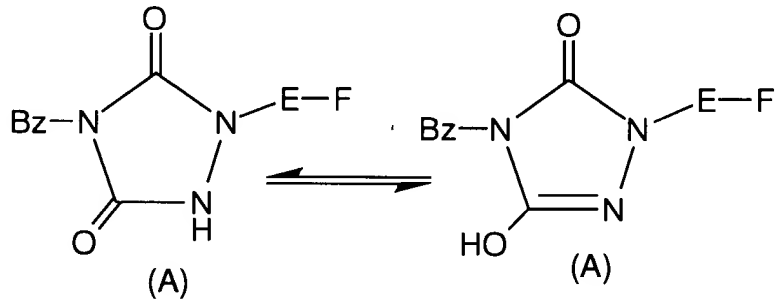
which can tautomerize to

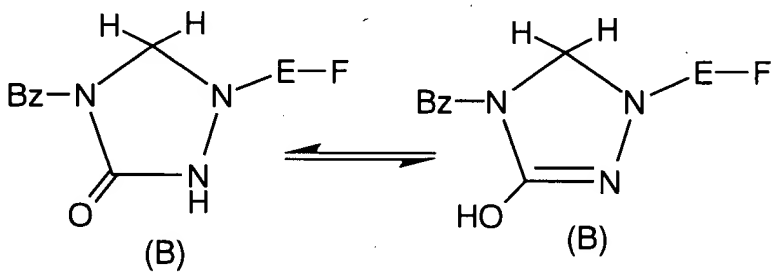


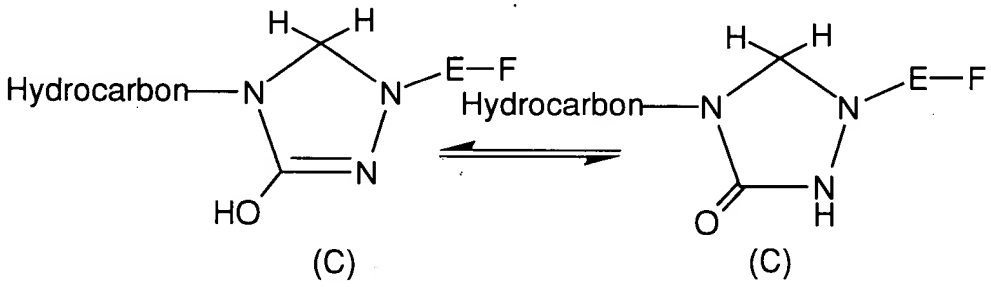
III III-A

The above three systems are heteroaromatic since they can tautomerize to a two double bonded ring structure.

However, Formulas A, B and C recited by the Examiner, are <u>not</u> heteroaromatic since they <u>cannot</u> tautomerize to form a non-quaternary <u>two</u> double bonded ring as illustrated below;







Thus, Structures A, B and C can only tautomerize to yield a singly double bonded heterocycle, which is <u>not</u> aromatic.

As stated above, the key here is that, when two (2) of the ring nitrogen atoms in a 1,2,4-triazolidine system are substituted with hydrocarbon radicals, the molecule cannot tautomerize to yield a two double bonded ring system which is aromatic.

Thus, Robertson, in which the 1,2,4-triazolidine ring is di-N-substituted, does not teach heteroaromatic rings and conversely, applicants' disclosure does not include non-heteroaromatic rings, and thus Robertson does not teach or suggest applicants' compounds.

Reconsideration of this point is respectfully requested.

The rejection of claims 1 through 8 under 35 USC 103 over Robertson under 35 USC 103 is maintained by the Examiner.

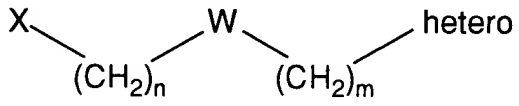
Examiner states --

> Robertson taught both aromatic and non-aromatic ring system can be employed in similar type of compounds for treating migraines. Specifically, the dioxoimidazolinyl moiety is considered aromatic based on tautomerism. (See Katritzky Heterocyclic Chemistry p. 233). In addition, the comparative results submitted by applicants showing IC_{50} for (1) and (2) (Paper No. 6, p. 2) are not persuasive. Compound (2) is not example 5. Example 5 has a dimethyl substitution of the amino groups.
>
> The comparative data cannot overcome the rejection because:
> (1) Robertson taught heteroaromatic as well as heteroaliphatic ring system for W of Robertson's.
> (2) While the Declaration provided evidence that compound (2) is superior than Robertson's species, this superiority cannot be extrapolated to the generic claims which encompassed both heteroaromatic and heteroaliphatic rings.
> (3) The comparative result is limited to that aromatic triazoles is superior then aliphatic triazoles. --

The Examiner's rejection is respectfully traversed and deemed moot by the cancellation of claims 1 through 8 and reconsideration is respectfully requested.

However, the Examiner's comments regarding the structural chemistry are not correct and rebuttal is being made for the record.

Basically, as stated above, Robertson does not teach both aromatic 1,2,4-triazole and non-aromatic 1,2,4-triazolidine ring systems; he only teaches 1,2,4-triazolidine rings. In his disclosure on page 1 of the patent, the heterocyclic ring W is depicted as:



Thus, W of Robertson is a disubstituted heterocyclic ring system, but cannot be heteroaromatic and quaternary.

As shown above, where 1,2,4-triazolidine is substituted on two ring nitrogen atoms with 2 alkyl or 2 carbon attached substituents, the ring cannot be aromatic.

This is supported by the disclosure in Katritzky, p. 233, which shows the tautomeric form of compounds 313, 315, 317, 321, in which the aromatic tautomeric form contains two double bonds.

However, as seen for compound 325, substitution on both ring N atoms has rendered the ring non-aromatic since only one double bond can be present in the ring and there are no other possible tautomeric forms.

This is precisely the case in Robertson. His 1,2,4-triazolidine compounds are di-N-substituted and thus are not heteroaromatic.

Also, the Examiner's comments regarding the comparative data are rebutted.

The one structural difference between Compounds (1) and (2) in the Street Affidavit lies in the hetero-aromatic ring of (2) taught by applicants and the non-aromatic ring of (1) taught by Robertson. This is the structural feature which Examiner is asserting to be equivalent. However, the results show that they are not equivalent. Thus, this is a *prima facie* showing of an unobvious advantage

of the heteroaromatic ring of (2) over the non-aromatic ring (1) of Robertson, and is a valid comparison of the two different structural features which supports patentability of applicants' compounds. As the Examiner suggests, the N,N-dimethylamino analogue (Example 5) shows even a greater effect. However, Compound 2, which is Step 4 in Example 5, would not have provided a meaningful comparison against Compound (1) since it has two different structural features from (1), the heteroaromatic ring and the dimethylamino group. Thus, Compound (2) is a much better compound for direct comparison purposes.

Further in rebuttal of Examiner's numbered comments:

(1) Robertson does not teach heteroaromatic 1,2,4-triazole ring systems as does applicants.

(2) The superiority of the Comparative Example (2) can be extrapolated to the generic claim of claim 1 since it encompasses heteroaromatic triazoles, which is the unexpected feature of the Comparative Example being a common structural feature of the broad claim 1, i.e., the 5-membered heteroaromatic ring.

(3) The comparative result should not be limited to aromatic triazoles, but should encompass the other 5-membered heteroaromatic rings which are disclosed and enabled in the specification as well.

Examiner further states --

> Claims 4 and 6 are rejected under 35 USC 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.
>
> Claim 4 embraced tetrazoles which are not in the base claim. Please note that the proviso statement requires one of Y^2 or Z^1 is "N", the other can be C or N, therefore, triazoles and tetrazoles.
>
> Claim 6, imidazolyl and tetrazolyl compounds are not in the base claim 1.
> --

These rejections are deemed moot since claims 4 and 6 have been canceled by this amendment and reconsideration is requested.

Claims 1 through 5, 8 and 13 are being rejected under 35 USC 112, first and second paragraphs, allegedly as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner states --

What does "cyclic hydrocarbon up to 18 carbon atoms" mean" Does this moiety including norbornyl or camphanyl? How are these compounds made? (1st para.)

If this term is ascribing only those as disclosed on p. 5 specification, the term lacks the particularity and specifity as required by the 2nd paragraph.

What does the term "a heterocyclic group containing up to 18 carbon atoms and at least one hetero atom selected from oxygen, nitrogen and sulfur" mean? Does this moiety include trithiazoles? How can such trithiazolyl compounds be made into pharmaceutical compositions? (1st para.) How do those diversified heterocyclic group containing compounds fit into the 5-HT_{1A} or $5HT_{1C}$ receptor sites which has "quite strict" structural requirements in its ligation. (See Glennon ref. 1449, p. 4 right col., last par.). (1st para. rejection).

The term "aryl" is unclear. Does this term include 20 or more fused aromatic rings? for which enabling teaching is lacking (first par.). If this term is ascribing those as disclosed on p. 6, specification, the term lacks the particularity and specifity as required by the 2nd paragraph.

The term =N.G is ambiguous. The bonding to G should be consistent with the other bonding as a "-" not a period.

The term "migraine and associated clinical conditions" is unclear. What conditions are "associated clinical concitions"? it is recommended that the particular conditions be specifically pointed out as disclosed on p. 1 specification.

The Examiner's rejection is respectfully traversed. Since claims 1 through 5, 8 and 13 have been canceled the above rejection is deemed to be moot and reconsideration is requested.

Claim 13 has been amended and rewritten as claim 19, which is not deemed to contain any of the objected to language listed above by the Examiner.

It is deemed that the language inserted into claim 19, to more particularly define and displace "associated clinical conditions" is supported on page 1, lines 17 through 20 of the specification and reconsideration is requested.

Examiner states that claims 9 through 12 are allowable, because the Declaration showed superior IC_{50} for unsubstituted aromatic triazolyl species.

Based on this statement it is deemed that claims 9 through 12, 14 and 19, which remain in this application, are also allowable on the same basis as stated above.

Examiner states that claims 7 and 14 through 18 are objected to because they are dependent on rejected base claims. Claims 7 and 15 through 18 are being canceled. Remaining claim 14 is dependent on newly-added claim 19, which is actually amended old claim 13, and deemed to be allowable. Reconsideration is respectfully requested.

Applicants' claims 9 through 12, 14 and 19 are now deemed to be in condition for allowance and Examiner is requested to pass this case to issue.

Respectfully submitted,

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